Testosterone is the most abundant active sex steroid in both pre and post-menopausal women and is present at levels three-four times that of oestrogen. Testosterone is produced directly from the adrenal glands and the ovaries in approximately equal amounts. Additionally, the ovaries and adrenal glands produce the androgen precursors DHEA and androstenedione. These androgen precursors are converted in the peripheral circulation and target cells to testosterone. They are responsible for around 50% of circulating testosterone.

In women, testosterone levels decline gradually with age, primarily due to reduced adrenal production, so that by the age of 40 levels are half that of a 20-year old. Unlike oestrogen, testosterone levels do not show a precipitous drop during natural menopause and the ovaries remain an important source of androgen production in postmenopausal women. However, following surgical menopause, testosterone levels drop by up to 50%.

Most testosterone circulates bound to sex hormone binding globulin (SHBG) or albumin. Only approximately 1-2% circulates as free testosterone – the biologically active form. Factors which increase SHBG levels (such as oral oestrogen) can therefore reduce free testosterone. Testosterone may act directly in target tissues or indirectly, though peripheral conversion to oestradiol by the aromatase enzyme.

Low sexual desire is a common problem across all ages. Distressing low sexual desire, (also termed hypoactive sexual desire disorder or HSDD) is estimated to affect 9-15% of menopausal women. HSDD has an important impact on physical and psychological wellbeing and has been associated with low self-esteem, depression and relationship difficulties.

Female sexual function is the result of a complex interplay between psychological, social and physiological factors. Assessment of low sexual desire should take into account the many possible aetiologies such as stress, relationship difficulties, menopausal status, medical comorbidities and drugs.

In menopausal women, hormonal deficiencies can have a profound effect on sexual function, with oestrogens and androgens each playing a crucial role. The effects of oestrogen deficiency both locally (vulvovaginal atrophy) and systemically (mood disturbance, poor sleep) can have a detrimental effect on sexual function. Therefore, before considering menopausal testosterone therapy, it is usually recommended to ensure adequate local and systemic oestrogen replacement. Oral oestrogen may exacerbate testosterone deficiency by increasing SHBG levels. By avoiding first-pass hepatic metabolism, transdermal oestrogens (such as patches or gels) do not affect SHBG levels and therefore may be preferable in women who have low sexual desire.
Testosterone replacement has long been recognised to be of benefit for low sexual desire. In the past, oral, intramuscular or subcutaneous preparations were used, but these achieved supraphysiological testosterone levels. In recent years, there has been a move towards more physiological replacement via the transdermal route, using patches or gels.

There is now significant data in support of transdermal testosterone therapy for women with low sexual desire. Much of the evidence has come from studies using the transdermal testosterone patch. Unfortunately, the testosterone patch has now been withdrawn for commercial rather than safety reasons, but similar benefits have been demonstrated with testosterone gel.

The testosterone patch Intrinsa only received a UK Marketing Authority license for use in surgically menopausal women on HRT, yet data is available that demonstrates the efficacy of transdermal testosterone in a range of populations, including naturally menopausal women on HRT and postmenopausal women not on concomitant HRT. It has also been shown to have benefit in women with SSRI or SNRI associated low libido.

Current UK guidelines recommend consideration of testosterone replacement in either naturally or surgically menopausal women who have low sexual desire despite HRT.

Androgen receptors are found throughout the body and therefore testosterone has many important roles in normal female physiology. It is well recognised that androgen deficiency can cause a variety of symptoms including low sexual desire, reduced sense of well-being, low mood, poor energy, reduced cognition, insomnia, vasomotor symptoms and joint pain.

In addition to improved sexual function, studies have shown benefit from testosterone replacement to quality of life, energy levels, mood, wellbeing, cognitive function and bone density. Furthermore, there is emerging data to suggest a role for intravaginal testosterone for the treatment of vulvovaginal atrophy, but further studies are needed.

Testosterone is a notoriously difficult hormone to measure in women, and commonly used assays lack accuracy at the lower testosterone levels found in women compared to men. Additionally, there is a lack of correlation between testosterone levels and symptoms of androgen deficiency. Current guidelines do not therefore recommend using testosterone levels diagnostically in women with low libido, but they do play a role in monitoring treatment.

As testosterone is prescribed off-label, it is usually recommended to measure testosterone levels at baseline and again after two-three months of treatment to exclude hyperandrogenaemia. Thereafter, testosterone levels should be assessed every six months. Ideally, levels should be kept within the physiological range to minimise risk of side effects.

When measuring serum testosterone, both total testosterone and SHBG levels should be assessed. Free androgen index can be the most clinically useful measurement and can be calculated as:

\[ \text{Free androgen index} = \frac{\text{total testosterone} \times 100}{\text{SHBG}} \]

Reference ranges vary depending on the laboratory but upper limits are usually considered as 3.5nmol/L for total testosterone and 5% for FAI.
MENOPAUSE

Myth 6 - Now that the testosterone patches have been withdrawn there are no testosterone preparations that can be prescribed

Unfortunately, the transdermal testosterone patches and subcutaneous implants that were licensed in the UK have been withdrawn from the market for commercial rather than safety reasons. At present, no preparations designed for use in women are available in the UK, Europe or USA. In Australia, testosterone cream is licensed for use in women (Androfeme), but there are no immediate plans for this to be available in the UK.

Analysis of US testosterone prescriptions showed that 21% of prescriptions for male testosterone products were used by women, highlighting the need for female testosterone products.

In the UK, male testosterone gel products such as Testim or Tostran can be prescribed off-label by specialists (see Table 1).

Myth 7 - Testosterone replacement has a high risk of side effects

When discussing testosterone replacement, the most frequent patient concern is regarding the risk of side effects such as excess hair growth. Androgenic side effects include acne, hirsutism, alopecia and rarely virilisation (voice deepening and clitoromegaly) and are associated with supra-physiological testosterone levels. These side effects were more frequent with the older forms of testosterone replacement, including oral or intramuscular preparations, and are uncommon with transdermal preparations.

Meta-analysis of studies involving transdermal testosterone has shown no increase in facial hair, alopecia or voice deepening. Side effects such as hirsutism and acne are usually mild and dose dependent. Should they occur, dose reduction is usually sufficient but, if persistent, will resolve on treatment discontinuation.

Myth 8 - Testosterone replacement causes aggression

A common perception is that testosterone is associated with aggression, yet the available data in women is conflicting. Importantly, there are no studies which have shown an increase in aggression levels in women using transdermal testosterone replacement. Even in older studies using supra-physiological dosing, aggression was not a reported side effect. On the contrary, testosterone has been associated with an improvement in mood, irritability and anxiety levels.

TABLE 1: THE BRITISH MENOPAUSE SOCIETY (11) RECOMMENDATIONS FOR TESTOSTERONE REPLACEMENT STATE:

- Testosterone gels licensed for male use are available in 50mg/5mL sachets or tubes
- Unlicensed prescribing by specialists is an option for female androgen replacement in women with distressing low libido or tiredness
- A reduced dosage of 0.5 to 1.0mL/day or 1/4 sachet/tube on alternate days should be used
Due to gender differences in the incidence of cardiovascular disease, it has traditionally been thought that testosterone has an adverse effect on the cardiovascular (CV) system. Women with polycystic ovarian syndrome and elevated androgen levels are known to have increased risk of CV disease, but in postmenopausal women the data is more conflicting. Most data seems to point to a u-shaped curve for endogenous testosterone levels and CV risk, with both low and high androgen levels associated with increased CV risk. Older studies suggested a possible adverse effect from testosterone replacement on CV risk factors, but these studies used supraphysiological dosing via oral or parenteral routes. These findings cannot therefore be applied to physiological replacement via the transdermal route. Studies using transdermal testosterone have shown no adverse effect on risk factors for CV disease including lipid profile, blood pressure, glucose metabolism or weight distribution. Pooled analysis from five of the testosterone patch safety studies showed no increase in CV events in women using testosterone.

**Myth 9 - Testosterone is bad for the heart**

Both endogenous and exogenous testosterone can be converted peripherally into oestradiol and therefore concerns have been raised about a potential association with oestrogen sensitive cancers. Two older observational studies reported an increased incidence of breast cancer in testosterone users, yet both studies had methodological flaws and did not adequately adjust for confounding factors such as oestrogen levels and body mass index. Multiple other observational studies have shown no association between testosterone use and breast cancer incidence. Randomised controlled data has shown that transdermal testosterone has no adverse effects on breast cell proliferation or mammographic density and studies have even show benefit from androgen therapy as an adjunctive treatment in women with breast cancer.

Androgens have an inhibitory effect on the endometrium, but few long-term studies have investigated the effect of menopausal testosterone replacement on the endometrium. To date, randomised controlled trial and observational data in women using transdermal testosterone has shown no increased incidence of endometrial hyperplasia or cancer.

**Myth 10 - Testosterone is associated with increased risk of breast and endometrial cancer**

Testosterone is increasingly used as part of menopausal HRT regimens due to the accumulating evidence of the potential benefits, particularly on sexual function and general wellbeing. The short-term safety is well established and, overall, the data is reassuring regarding the long-term safety of transdermal testosterone, although more studies are needed. There are currently no products designed for use in women in the UK that can be prescribed and, at present, off-label prescribing of male testosterone products is the most commonly used option.

### Conclusion

Testosterone is increasingly used as part of menopausal HRT regimens due to the accumulating evidence of the potential benefits, particularly on sexual function and general wellbeing. The short-term safety is well established and, overall, the data is reassuring regarding the long-term safety of transdermal testosterone, although more studies are needed. There are currently no products designed for use in women in the UK that can be prescribed and, at present, off-label prescribing of male testosterone products is the most commonly used option.

### References